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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/808,827	02/28/1997	WALTER HENRY GUNZBURG	GSF97-01A	6837

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EXAMINER	
BRUSCA, JOHN S	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 03/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	08/808,827	SALLER ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7,9-26,28,29 and 31-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,7,9-26,28,29 and 31-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Drawings

1. The drawings were received on 22 December 2003. These drawings are acceptable.

Claim Rejections - 35 USC 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 recite the phrase "a heterologous promoter which is not related to a promoter from a retrovirus upon which the retroviral vector is based." In the arguments filed 22 December 2003, on page 16, the applicants point to support for the amendment at page 10, lines 4-16 and Examples 1-3, however the pointed to sections of the specification discuss only heterologous promoters, the Mouse Mammary Tumor Virus promoter, and the Whey Acidic promoter, and do not discuss the claimed genus of promoters as quoted above.

For the reasons discussed below the metes and bounds of the limitation are indefinite and it is not clear whether MMTV promoters are members of the claimed genus. The Applicants

have failed to a description of the claimed genus of promoters in the instant specification at the time of filing. As such the rejection is maintained.

4. The rejection of claims 1, 5, 7, 9-26, 28, 29, and 31-101 under 35 U.S.C. § 112, second paragraph as indefinite for recitation of the limitation "said one or more sequences selected from coding sequences" is withdrawn in view of the amendment filed 22 December 2003.

5. The rejection of claims 1, 5, 7, 9-26, 28, 29, and 31-101 under 35 U.S.C. § 112, second paragraph as indefinite because they read on vectors that comprise only non coding sequences that further comprise promoters that regulate only coding sequences is withdrawn in view of the amendment filed 22 December 2003.

6. The rejection of claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 under 35 U.S.C. § 112, second paragraph as indefinite for recitation of the phrase "reduced chance of recombination" is withdrawn in view of the amendment filed 22 December 2003.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 are indefinite for recitation of the phrase "a heterologous promoter which is not related to a promoter from a retrovirus upon which the retroviral vector is based " because the metes and bounds of the claimed promoter are unclear.

Claims 5 and 16 recite the limitation "said heterologous vector." There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses, including leukemia and sarcoma retroviruses. Couture et al. shows on page 669 column 2 that the first 40 nucleotides of the original vector are retained in the substitution of the U3 region. The vector of Couture comprises a chloramphenicol acetyl

transferase marker gene and a neomycin resistance gene. Couture et al. shows in the abstract that after packaging, the substituted U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. states in the second paragraph of the Results section on page 669 that U3 regions are bound by cellular factors. Couture et al. shows in Table 3 that their chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors. Couture et al. does not show a vector comprising a multiple cloning site in the U3 region.

Faustinella et al. shows in figure 1 Moloney murine leukemia retroviral vector pS3. pS3 comprises a partial deletion of the 3' U3 region, into which has been inserted a polylinker with unique cloning sites, for example the Bsa AI site and the Nae I site used to construct the vectors of figure 2.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of Couture et al. by adding the multiple cloning site of Faustinella et al. because Faustinella et al. shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector.

11. Claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella

et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mee et al.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above does not show mouse mammary tumor virus (MMTV) promoters or regulatory elements.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above by insertion of an MMTV promoter region in a deleted 3' U3 region of a retroviral vector because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types.

12. Claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-36, 38, 39, 42-49, and 51-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mehigh et al.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above does not show cellular promoters or regulatory elements.

Mehigh et al. shows a retroviral vector comprising a whey acidic acid protein (WAP) promoter. Mee et al. states in the abstract that their vector allows for inducible expression from the WAP promoter of an operably linked gene in MBDK cells and may prove useful as a delivery system for peptides in cattle to increase milk production.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above by insertion of a WAP promoter region in a deleted 3' U3 region of a retroviral vector because Mehigh et al. shows that such vectors are inducibly expressed and may allow for increased milk production in cattle.

13. Claims 1, 13, 14, 33, 40, 41, 56, 63, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of:

1)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above,

2)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mee et al. as applied to claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78,

3) Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mehigh et al. as applied to claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-35, 38, 39, 42-49, and 51-55 and further as evidenced by Miller et al. and Panganiban et al.

The three combinations of references cited above do not explicitly show an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Couture et al. shows in figure 1 a retroviral vector LCSN and a derivative of LCSN. Couture et al. shows in the Methods section on page 668 that their vectors are derivatives of the vectors of Miller et al.

Miller et al. shows in figure 2 that their vectors retain the phi+ packaging sequence, but lack the gag, pol, and env genes of a replication-competent retrovirus.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

Therefore the vectors of claims 13 and 14 are taught by the above cited combinations of references as evidenced by Miller et al. and Panganiban et al.

14. Claims 1, 10, 33, 37, 56, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of:

1)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above,

2)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mee et al. as applied to claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78,

3) Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mehigh et al. as applied to claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-35, 38, 39, 42-49, and 51-55 and further in view of Price et al.

The three combinations of references cited above do not explicitly show retroviral vectors derived from BAG vectors.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of the above cited combinations of references by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

15. Claims 17, 20, 21, 26, 28, 43, 50, 51, 52, 53, 66, 73, 74, 75, and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of:

1)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above,

2)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mee et al. as applied to claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78,

3) Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mehigh et al. as applied to claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-35, 38, 39, 42-49, 51-55, 79-82, 84, 85, 88-95, and 97-101,

and further in view of Longmore et al. and Kay et al.

The three combinations of references cited above do not show use of retroviruses in animals.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of the combinations of references cited above to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal.

16. Applicant's arguments filed 22 December 2003 have been fully considered but they are not persuasive.

The applicants state that Couture et al. teaches away from the use of heterologous promoters, however Couture et al. shows that a variety of heterologous promoters have activity in the exemplified vectors (see tables 1-3). Couture et al. teaches in the abstract and throughout that different promoters may be used for preferential expression in desired cell types. The applicants argue that Couture et al. shows only substitution of related promoters that are not part of the claimed vectors, however as discussed above the limitations of "promoters which are not related to a promoter from a retrovirus upon which the retroviral vector is based" is indefinite and does not serve to exclude the promoters used by Couture et al. The applicants argue that Mee

et al. does not show insertion of an MMTV promoter in the vector of Couture et al., however the combination of the showing of the utility of the MMTV promoter by Mee et al. with the showing of the utility of the vector of Couture et al. makes the combination of the promoter of Mee et al. and the vector of Couture et al. obvious. The applicants argue that Mehigh et al. does not show insertion of a WAP or MMTV promoter in the vector of Couture et al., however the combination of the showing of the utility of the WAP and MMTV promoters by Mehigh et al. with the showing of the utility of the vector of Couture et al. makes the combination of the promoters of Mehigh et al. and the vector of Couture et al. obvious. The applicants argue that Miller et al. and Panganiban et al. do not show the vectors of Couture et al. with altered retroviral genes or altered integration sequences, however Miller et al. and Panganiban et al. serve to show that the LCSN vectors upon which the vectors of Couture et al. are based have partially deleted integration sequences. The applicants argue that Price et al. does not show use of beta galactosidase reporter genes in the vector of Couture et al., however the combination of the showing of the utility of the reporter genes for marking vector-infected cells by Price et al. with the showing of the utility of the vector of Couture et al. makes the combination of the reporter gene of Price et al. and the vector of Couture et al. obvious. The applicants argue that Kay et al. and Longmore et al. do not show expression of therapeutic genes in the vector of Couture et al., however the combination of the showing of the utility of expression of therapeutic genes in retroviral vectors by Kay et al. and Longmore et al. with the showing of the utility of the vector of Couture et al. makes the combination of the therapeutic genes of Kay et al. and Longmore et al. and the vector of Couture et al. obvious.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is (517) 272-0714. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (517) 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

John S. Brusca
Primary Examiner
Art Unit 1631

jsb